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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/671,260	09/25/2003	Dorte Lunoe Dunweber	6546.200-US	6556

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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 03/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/671,260	DUNWEBER ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/6/04, 4/8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT TO PRIORITY, IDS, STATUS OF THE APPLICATION AND CLAIMS

1. Acknowledgement is made of Applicant's claim for priority based on Danish Application No. PA 2002 01421 having a filing date 09/25/02. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The information disclosure statement (IDS) and Form PTO-1449 filed 04/08/04 and 02/06/04, respectively are acknowledged, entered and considered. Claims 1-37 are now pending in the application.

SEQUENCE COMPLIANCE WITH OFFICE ACTION

2. This application contains sequence disclosures at page 13 and claim 35 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a((1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 C.F.R. § 1.821 through 1.825 for one or more of the reasons set forth on the attached form "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequences And/Or Amino Acid Sequence Disclosures". Wherein attention is directed to paragraph(s) §1.82 (c) and (e). Although an examination of this application on the merits can proceed without prior compliance, compliance with the Sequence Rules is required for the response to this Office action to be complete.

OBJECTION TO THE CLAIMS

3. Claims 27-34 are objected in the recitation "RP-HPLC" (claims 27-31), "GLP-1" (claims 32-34) and "GLP-2" (claim 32), respectively. Use of the full terminology at least in the first occurrence would obviate this objection.

CLAIM REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, 15 and 25 are indefinite in the recitation "....selected from....." because it is not clear if Applicant intends a Markush format. If Applicant intends to use a Markush format, then, the Office recommends to use of the phrase ".....selected from the group consisting of....." in listing species to ensure the Markush group is "closed".(See e.g., claims 7, 12, 26, 32 and 34).

Claim 12 is indefinite and confusing in the recitation "The method according to any one of claims 9" because there is only one claim 9. Amendment of the claim to recite "The method according to claim 9" is suggested (See e.g., claims 10 and 11).

CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

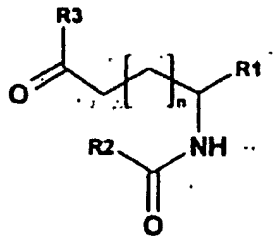
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/55119 taken with Zivanovic et al (Biomedical Chromatography, Vol. 14, pp. 56-57, 2000).

The reference of WO 00/55119 ('119 patent) like the instantly claimed invention discloses a method for acylating one or more amino groups of a peptide (or protein), the method comprising:

a) reacting a peptide (or protein) having at least one free amino group with an acylating agent of the general formula I



wherein

n is 0-8;

R^1 is COOH;

R^2 is a lipophilic moiety, preferably selected from C_{3-39}-alkyl, C_{3-39}-alkenyl, C_{3-39}-alkadienyl and steroidal residues; and

R^3 together with the carboxyl group to which R^3 is attached designate a reactive ester or a reactive N-hydroxy imide ester.

and R^4 is selected from hydrogen, C_{1-12}-alkyl and benzyl, under basic conditions in a mixture of an aprotic solvent and water; and

b) if R^4 is not hydrogen, saponifying the acylated peptide ester group ($COOR^4$) under basic conditions in order to obtain an N-acylated peptide (or an N-acylated protein). See e.g., Summary of the Invention, page 12 under Aspect 1 and claim 1 of the '119 patent as directed to claim 1 of the instant invention.

Acylation of peptides and proteins by the introduction of lipophilic acyl groups to reduce the *in vivo* clearance rate is known in the art as acknowledged on page 2, paragraph 1 in the instant specification. However, on page 10, lines 27 to page 11 lines 3, the '119 patent discloses various aprotic polar solvents including N-methyl-2-pyrrolidone, tetrahydrofurane (THF) and dimethylsulfoxide (DMSO) of which N-methyl-2-pyrrolidone is especially preferred, and the ratio between the aprotic polar solvent and water (e.g., N-methyl-2-pyrrolidone and water) is typically 1:10 to 10:1, in particular 1:5 to 5:1, especially 1:1 to 3:1, as such meet the limitations of claims 6 -8. Further, on

pages 12 and 13 the prior art discloses various aspects of the invention, which reads on the instantly claimed invention. For example, Aspect 2. A method according to aspect 1 (i.e., as claimed in claim 1 of the instant invention), wherein R^4 is hydrogen (meets the limitation of claim 14). Aspect 3. A method according to aspect 1, wherein R^4 is selected from C_{1-8}-alkyl and benzyl (meets the limitation of claim 15). Aspect 4. A method according to aspect 1, wherein the R^3 together with the carboxyl group to which R^3 is attached designate a reactive N-hydroxy imide ester (meets the limitation of claim 16). Aspect 6. A method according to aspect 1, wherein the pH of the reaction mixture is in the range of 9-13 (meets the limitation of claims 18 and 19). Aspect 7. A method according to aspect 1, wherein the temperature of the reaction is in the range of 0-50^0 C (meets the limitation of claim 22); and on page 9, line 10, the reference states that the reaction is typically performed at a temperature in the range of 0-50^0 C, e.g., 5-30^0 C such as room temperature, which overlaps with claimed ranges of claims 22-24. Aspect 8. A method according to aspect 1, wherein the acylated ester is saponified at a pH value in the range of 10-14 (meets the limitation of claim 17). Aspect 9. A method according to aspect 1, wherein R^2 is selected from C_{3-39}-alkyl, C_{3-39}-alkenyl, C_{3-39}-alkadienyl and steroidal residues (meets the limitation of claim 25). On page 7, lines 31-35, the '119 patent states that the term "steroidal residue" is intended to mean a lipophilic group which together with the carbonyl group to which R^2 is attached is derived from a steroid carboxylic acid, i.e., a tri-, tetra- and pentacyclic, full saturated or partially unsaturated C_{18-36}-hydrocarbon. Examples of such groups R^2-C(=O)- are lithocholoyl and hexadecanoyl, and as such meets the limitation of claim 26.

With respect to the limitation of claim 36, the prior art clearly uses a buffer, which is suitable for maintaining constant pH during reaction, and as such meets the limitation of claim 36. In regard to the limitation of claim 37, wherein the peptide acylated is not insulin or an analogue thereof, the reference on page 4, lines 12-23 cites various peptides which is not insulin or an analogue thereof by stating that it is generally believed that the present invention is useful for the introduction of lipophilic acyl group into any peptide (or protein) in order to reduce the *in vivo* clearance rate. Examples of such peptides and proteins are ACTH, corticotropin-releasing factor, calcitonin, etc., and as such meets the limitation of claim 37. Further, the limitations recited in claims 1-4 and 6-9 of the '119 patent is substantially the same with the instantly claimed invention of claims 1, 14-16, 18 and 19, 22, 17 and 25, respectively. Furthermore, on page 4 lines 31 to page 6, lines 13 and claims 11and 12 of the '119 patent clearly teaches the acylation of peptides such as GLP-1, GLP-2, exendin-3, exendin-4, glucagons, insulin, analogues thereof and derivatives of any of the forgoing, and as such meets the limitations of claims 32-35.

The primary reference of WO 00/55119 differs from claims 1-37 in not teaching the use of a) an aqueous mixture containing less than 10% w/w, or less than 8% w/w, or less than 5% w/w or less than 3% w/w aprotic polar solvent (in each situation), b) the addition of an acid such as sulphuric acid, methanesulphonic acid and trifluoroacetic acid to stabilize the reaction mixture of a solution containing acylating agent, and c) the purification of the peptide by Reverse Phase-High Performance Liquid Chromatography (RP-HPLC). Although, the primary reference does not disclose the exact percentage

ranges of aqueous mixture and aprotic polar solvent in the manner claimed in claims 1-4, however, on page 11, lines 1-3, the reference states that the ratio between the aprotic polar solvent and water (e.g., N-methyl-2-pyrrolidone and water) is typically 1:10 to 10:1, in particular 1:5 to 5:1, especially 1:1 to 3:1. In view of these ratios which discloses the aprotic polar solvent and water ratio, it would be obvious to one of ordinary skill in the art to which this invention pertains to optimize the required ratio of aprotic polar solvent and water in order to have optimum condition for the acylation reaction to be performed in an aqueous mixture.

In regard to the addition of an acid such as sulphuric acid, methanesulphonic acid and trifluoroacetic acid to stabilize the reaction mixture of a solution containing acylating agent, although, the '119 patent does not teach the addition of the recited acids, however, the '119 patent clearly teaches on page 11, lines 17-18 by stating the pH value may further adjusted using acids, e.g., acetic acid, and bases; on Example 1, shows the addition of an acid such as 0.2 M hydrochloric acid; Example 6, demonstrates the addition of 1.0 M acetic acid to adjust the pH solution to 8; and Examples 7 and 8 adjusted the pH of the reaction mixtures to 6.0 and 7.45, respectively by addition of 1 M acetic acid. Thus, it is within the ordinary skill of the art to which this invention pertains to select/optimize the appropriate acid (e.g., acetic acid or HCl or H_2SO_4, etc.,) for adjusting the pH solution (design of choice) which are widely known in the art and widely employed as an adjuster of pH value in a given mixture solution (i.e., in the instant case for adjusting the aprotic polar solvent mixture). Therefore, such selection/optimization of an acid of interest for adjusting the pH of a mixture solution for

the intended purpose of having optimum pH clearly would be routine to a person of ordinary skill in the art to which this invention pertains at the time the invention was made.

Wit respect to the purification of the peptide by Reverse Phase-High Performance Liquid Chromatography (RP-HPLC), the '119 patent on page 9, lines 18-19 suggests various purification routes to remove precipitated solvent material by filtration, evaporation of the solvent under reduced pressure, and resuspension of the product. Further, on page 11, lines 20-24, the '119 patent states that the reaction can be monitored by HPLC and the product is typically isolated and purified by HPLC. Furthermore, on page 12, lines 1-2, the '119 patent states that after reactions, the product is purified, e.g., by precipitation at isoelectric pH and/or by preparative HPLC. Also, in Example 6, the '119 patent concludes by stating that final purification of the product was obtained by column chromatograph. Although, the '119 patent suggest the use of HPLC for purification of the peptide, and in view of this, one of ordinary skill in the art would have understood that HPLC purification needed the application of the RP-HPLC to obtain a peptide of sufficient purity; therefore, one of ordinary skill in the art would be motivated to look for chromatographic techniques which could assure the intended product to achieve the required purity. However, the secondary reference of Zivanovic et al states consequently the aim of this study was to propose an HPLC method for determination of a mixture of allylestrenol and α-tocopherol and to investigate the precision, accuracy and reproducibility of working conditions for RP-HPLC determination (See e.g. introduction). Further, the secondary reference teaches

the validation and application of the RP-HPLC method for the assay of allylestrenol and α-tocopherol wherein the method is sensitive, reproducible and rapid. The good recovery (i.e., 104.46% for allylestrenol and 93.47% for α-tocopherol) and relative standard deviation (RSD) values and the recovery percentages obtained indicate the method (i.e. RP-HPLC) to be suitable for routine analysis (See e.g., Table 1 and conclusion). Thus, RP-HPLC is a choice procedure, as pointed out by the secondary reference, and as such use of RP-HPLC is deemed to be obvious for one of ordinary skill in the art because the skilled artisan would reasonably have expected that the use of RP-HPLC of the secondary reference would have resulted in additional purification. Further, the advantages of using alternative chromatographic techniques including HPLC, which may encompass RP-HPLC is clearly suggested in the primary reference. Moreover, such features of purification by RP-HPLC are known or suggested in the art, as seen in the secondary reference, and including such features (i.e., RP-HPLC) into peptide purification methods of the primary reference, would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof for the intended purpose of producing pure N- acylated peptide. Thus, the combined teachings of the prior art clearly meet the limitations recited in claims 27-31.

Therefore, in view of the above and in view of the combined teachings of the references, the prior art clearly teaches methods for acylating peptides and proteins by introducing one or more acyl groups into a peptide or a protein thereof in the manner claimed in claims 1-37, absent of sufficient objective factual evidence or unexpected results to the contrary.

CITATION OF RELEVANT PRIOR ART

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hansen (U.S. Patent No. 5,905,140) teaches a method of introducing an acyl group into a peptide, particularly acylating the ε-amino group of a lysine residue contained in naturally occurring insulin or an analogue or a precursor thereof.

CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CAMPELL BRUCE can be reached on (571) 272 0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

Mohamed/AAM
3/10/06